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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/040,863	11/01/2001	Eric H. Holmes	20093A-002220US	3956

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EXAMINER
RAO, MANJUNATH N

ART UNIT	PAPER NUMBER
1652	9

DATE MAILED: 09/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/040,863	HOLMES ET AL.	
	Examin r	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-59 and 63-75* is/are pending in the application.

4a) Of the above claim(s) *55-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-54,59 and 63-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 48-59 and 63-75 are currently pending and are present for examination. Claims 48-54, 59, and 63-75 are now under consideration. Claims 55-58 remain withdrawn from consideration as being drawn to non-elected invention.

Election/Restrictions

Applicant's election of Group I, claims 48-54, 59, and 63-75 in Paper No. 7 with traverse is acknowledged. However, applicant did not distinctly and specifically point out the supposed errors in the restriction requirement.

Drawings

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

Specification

The disclosure is objected to because of the following informalities: The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable codes. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 59 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 59 depends from cancelled claims and therefore does not claim any definite subject matter.

Claim 53 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 53 recites the phrase "isolated or purified recombinant produced". It is not clear to the Examiner whether applicants are claiming an isolated and purified enzyme or a recombinant enzyme rendering the claim indefinite. Correction is required.

Claim 74 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim which depends from claim 71 which recites the amino acid sequence SEQ ID NO:10, recites that said amino acid sequence is encoded by SEQ ID NO:7. However, a perusal of the specification appears to indicate that SEQ ID NO:7 encodes the amino acid sequence SEQ ID NO:8. Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 52, 72-73, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for synthesizing a fucosylated molecule or a fucosyl-GM1 using an enzyme having α 1,2-fucosyltransferase (FT) with SEQ ID NO:8 or 10, does not reasonably provide enablement for such a method using any recombinant α 1,2-fucosyltransferase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 52, 72-73 are so broad as to encompass a method for synthesizing a fucosylated molecule or a fucosyl-GM1 using any recombinant α 1,2-fucosyltransferase. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of FTs broadly encompassed by the claims. It is well known in the art that there are specific types of FTs with separate substrate requirements, reaction condition requirements and acceptor molecule requirements and therefore not any or all recombinant FTs can be used to make specific products claimed in the above claims. Furthermore since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity

requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only two specific FTs. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides in the above method. The specification is limited to teaching the use of SEQ ID NO: 8 and 10 as the FTs for the above method but provides no guidance with regard to the use of making and using any recombinant FT including variants and mutants or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by this claim.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art

would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass method wherein all or any recombinant FT can be used because the specification does not establish: (A) a rational and predictable scheme for using any recombinant FT with an expectation of obtaining the desired biological function in a method leading to the synthesis of the products claimed; (B) and regions of the protein structure in SEQ ID NO:8 and 10 which may be modified without affecting its activity; (C) the general tolerance of FTs to modification and extent of such tolerance; (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including all or any recombinant FT in the claimed method. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of recombinant FTs having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 52-53, 72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 52-53, 72 are directed to method of making specific fucosylated products using any recombinant FTs. Claims 52-53, 72 are rejected under this section of 35 USC 112 because the claims are directed to a method wherein a genus of polypeptides including modified polypeptide sequences, modified by at least one of deletion, addition, insertion and substitution and fragments, that have not been disclosed in the specification, are used. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:8 and 10 has been provided by applicants which would indicate that they had possession of the claimed genus of polypeptides. The specification does not contain any disclosure of the structure of all the recombinant polypeptide sequences, including fragments and variants within the scope of the claimed genus. The genus of polypeptides claimed is a large variable genus including peptides which can have a wide variety of structure. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only two species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 48-51, 53-54 and 63-71, 74 are rejected under 35 U.S.C. 102(b) as being anticipated by Holmes et al. (JBC, 1983, Vol. 258(6):3706-3713). This rejection is based upon the public availability of a printed publication. Claims 48-51, 53-54 and 63-71, 74 of the instant application are drawn to a method of preparation of fucosylated compounds using a fucosyltransferase labeled as α1,2-fucosyltransferase which transfers fucose from GDP-fucose to a molecule having a terminal Galß1→3GalNAc moiety leading to the formation of Fucα1→2Galß1→3GalNAc or which transfers fucose from GDP-fucose to ganglioside GM_1 to form fucosyl-GM_1, wherein said enzyme comprises or consists of an amino acid sequence as depicted in either SEQ ID NO:8 or 10 or encoded by polynucleotide SEQ ID NO:7. Holmes et al. disclose the isolation and purification of such a fucosyltransferase from rat liver hepatoma and also methods of making the above products using the enzyme. However, the reference does not disclose that the amino acid sequence of the enzyme is either SEQ ID NO:8 or 10 or that it is encoded by a polynucleotide with SEQ ID NO:7. Since the enzyme isolated from Holmes et al. is from rat which has identical properties as that used in the above method, Examiner takes the position that the enzyme used in the claimed method and that disclosed in the reference is one and the same, (i.e., the amino acid sequence of the enzyme in the reference is that of either SEQ ID NO:8 or 10) based on inherency. Amino acid sequence of an enzyme is an inherent

characteristic of the enzyme just as it functional characteristic. Therefore Holmes et al. anticipate claims 48-51, 53-54 and 63-71, 74 as written.

Since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald* et al., 205 USPQ 594.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 52, 72-73, 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Holmes et al. (see above) as applied to claims 48-51, 53-54 and 63-71, 74 above, and further in view of the common knowledge in the art of protein purification and molecular cloning techniques. Claims 52, 72-73 and 75 are drawn to a method of preparation of fucosylated compounds using a recombinant fucosyltransferase labeled as α1,2-fucosyltransferase which transfers fucose from GDP-fucose to a molecule having a terminal Galß1→3GalNAc moiety leading to the formation of Fucα1→2Galß1→3GalNAc or which transfers fucose from GDP-fucose to ganglioside GM_1 to form fucosyl-GM_1, wherein said enzyme comprises or consists of

an amino acid sequence as depicted in either SEQ ID NO:8 or 10 or encoded by polynucleotide SEQ ID NO:7 or 9.

The reference of Holmes et al. which teaches the purification of the enzyme from crude rat liver extract as it applies to claims 48-51, 53-54 and 63-71, 74 has already been discussed above. Holmes et al. teach the purification of the above enzyme up to a point wherein it specific characteristics could be determined. The reference teaches the activity of said enzyme is induced in response to certain signals leading to the formation of specific fucogangliosides in rat livers. Using the above partially enzyme preparation taught by Holmes et al., it would have been obvious to those skilled in the art to purify the enzyme further using the highly improved protein purification techniques available at the time the instant application was filed, obtain the amino acid sequence and obtain a cDNA clone and arrive at a recombinant enzyme by using the common knowledge available in the art of molecular biology at the time of filing of the instant application. One of ordinary skill in the art would have been motivated to do so because Holmes et al. teach that this enzyme is induced during chemical carcinogenesis and therefore a recombinant form of the enzyme would be very useful for studying its properties extensively and such studies could have tremendous implication in understanding the mechanism of cancer in humans as well. One of ordinary skill in the art would have a reasonable expectation of success since Holmes et al. provide a pure enough material which can be used for further studies and the art is rich in several techniques and procedures in purifying the protein to homogeneity and obtaining its cDNA to make recombinant proteins. Therefore the above invention would have been *prima facie* obvious to one of ordinary skill in the art.

Double Patenting

Claims 48-54 of this application conflict with claims 48-54 of Application No. 09/999,672 (Published as US 2002/0127655 A1). 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

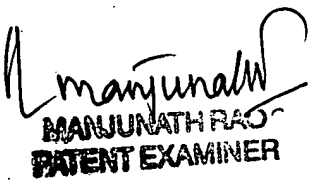
A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 48-54 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 48-54 of copending Application No. 09/999,672 (Published as US 2002/0127655 A1). This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



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9/27/03